Objections to the Specification

Applicants have removed the embedded hyperlinks in the specification and have submitted corrected drawings removing embedded hyperlinks. As such, Formal Drawings are being filed concurrently herewith, and entry of the Formal Drawings is requested.

Rejection of Claims 31-40 under 35 U.S.C. §112, Second Paragraph

Claims 31-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that Claims 31 and 36 are indefinite because the claims fail to include a positive process step relating back to the preamble.

Applicants have amended independent Claims 31 and 36 to include a positive process step relating back to the preamble as suggested by the Examiner, obviating the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 31-46 under 35 U.S.C. § 112, First Paragraph

Claims 31-46 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

It is noted that the Examiner states that the specification is enabling for methods of predicting the likelihood that an individual will have a myocardial infarction or coronary revascularization by determining the identity of the nucleotide at position 1186 of SEQ ID No. 3 wherein the presence of a C at position 1186 is indicative of an increased likelihood of a myocardial infarction or coronary revascularization as compared with an individual having a G at nucleotide 1186 and wherein the presence of a G at nucleotide 1186 is indicative of a decreased likelihood of having a myocardial infarction or coronary revacularization as compared with an individual with a C at nucleotide 1186. Claims 73-80 have been added which correspond to this subject matter.

Applicants have amended the claims to recite methods of **determining the likelihood** of vascular disease in a **human**, thereby obviating the portions of the rejection set forth at page 4, first paragraph through page 6, line 16.

In the remaining portion of the rejection, the Examiner states that the specification provides no teaching of the affect of a missense mutation at position 347 of SEQ ID NO: 4 on the activity of TSP-4 such that the aberrant protein leads to MI or coronary revascularization, and that without such teaching the skilled artisan would be unable to determine how or if the affect of the TSP-4 variant on TSP-4 activity would predictably result in a individual suffering from any vascular disease. The Examiner further states that the term vascular disease encompasses a large number of disorders that are not all related in terms of biochemical pathway or cause.

As described in the specification, Applicants conducted a study to determine pivotal genes associated with premature coronary heart disease. DNA samples were analyzed from patients with MI or coronary revascularization. TSP-1 and TSP-4 emerged as important SNP's associated with these diseases. TSPs are a family of extracellular matrix glycoproteins that modulate many cell behaviors. TSPs have broad function in the regulation of fibrinolysis, they bind to fibronectin and fibrinogen and are known to be involved in platelet adhesion and aggregation. Further, current research evidence indicates a link between platelet-thrombosis and the development of atherosclerosis. See specification page 32, lines 1-27. Although, the study as described in the instant application included only two disease groups, the broad reaching effects of TSPs as is described above make it reasonable to ascertain that TSPs play a role in the other disease states associated with vascular disease such as atherosclerosis, coronary heart disease, myocardial infarction, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism. The role of TSPs in vascular events and their role in MI and revascularization provide a reasonable correlation with other vascular disease states. Based on this evidence as a whole at the time of filing, the specification was enabling for the claimed invention.

The Examiner provided a post-filing date reference to demonstrate the unpredictability of associating a gene variant with **any** vascular disease. Applicants respectfully submit that the Examiner has taken statements from the reference out of context to expand on his point. The

cited reference merely teaches an autosomal genome-wide scan for coronary artery calcification loci in sibships at high risk for hypertension.

The statement regarding the limitations of use of symptomatic CAD endpoints such as sudden coronary death and MI is related to a study using **cholesterol guidelines** for identifying adults at increased risk of coronary disease. The article further states that although several CAD risk factors, including measures of lipid metabolism, obesity and blood pressure have a genetic basis, that may genes for coronary artherosclerosis lack symptoms and that one half of sudden coronary death and one half of **first** myocardial infarctions occur in persons without previous symptoms. The risk factors discussed in this reference are not thrombospondin polymorphisms such as is claimed by Applicants. Further, this study is not teaching the unpredictability of associating a gene variant with vascular disease based on the association of the variant with MI, but rather teaching the unpredictability of associating risk factors such as lipid metabolism, obesity, cholesterol levels and blood pressure with vascular diseases because they fail to identify a large proportion of individuals with symptomatic CAD endpoints such as sudden coronary death and MI. See paragraph 1, lines 6-9. In conclusion, this study provides no evidence that contradicts Applicants' claimed invention nor does the reference indicate that there is a lack of guidance in the specification or that the skilled artisan is required to carry out more than routine experimentation to make or use the claimed invention. As is shown in detail above, ample guidance is provided in the specification and by the knowledge of one of skill in the art to enable the skilled artisan to make or use the invention commensurate in scope with the amended claims.

In view of the above, Applicants submit that the invention as claimed is fully enabled by the specification. As such, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call Lisa M. Treannie, Esq. or the undersigned at (978) 341-0036.

Respectfully submitted,
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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 9, lines 7 through 17 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Fig. 3 shows a table providing detailed information about the SNPs identified herein. Column one shows the internal polymorphism identifier. Column two shows the accession number for the reference sequence in the TIGR database which can be found on the world wide web at [(http://www.] tigr.org/tdb/hgi/searching/hgi_reports.html. Column three shows the nucleotide position for the SNP site. Column four shows the gene in which the polymorphism was identified. Column five shows the polymorphic site and additional flanking sequence on each side of the polymorphism. Column six shows the type of mutation produced by the polymorphism. Columns seven and eight show the reference and alternate (variant) nucleotides, respectively, for the SNP. Columns nine and ten show the reference and alternate (variant) amino acids, respectively, encoded by the alleles of the gene.

Please replace the paragraph at page 14, line 25 to page 15, line 21 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The invention also relates to nucleic acid molecules which share substantial sequence identity to the variant alleles identified herein (or their complements) and which also comprise the variant nucleotide at the SNP site. Particularly preferred are nucleic acid molecules and fragments which have at least about 60%, preferably at least about 70, 80 or 85%, more preferably at least about 90%, even more preferably at least about 95%, and most preferably at least about 98% identity with

nucleic acid molecules described herein. The percent identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 60%, and even more preferably at least 70%, 80% or 90% of the length of the reference sequence. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, *Proc. Natl. Acad. Sci. USA, 90*:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) as described in Altschul *et al.*, *Nucleic Acids Res., 25*:389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, NBLAST) can be used. See the world wide web at [http://www.] ncbi.nlm.nih.gov. In one embodiment, parameters for sequence comparison can be set at score=100, wordlength=12, or can be varied (*e.g.*, W=5 or W=20).

Please replace the paragraph at page 48, lines 1-12 the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Publicly available sequences for a given gene were assembled into Gap4, which can be found on the world wide web: at [(http://www.] biozentrum.unibas.ch/~biocomp/staden/Overview.html [)]. PCR primers covering each exon were designed using Primer 3, which can be found on the world wide web at [(http://www-] genome.wi.mit.edu/cgi-bin/primer/primer3.cgi[)]. Primers were not designed in regions where there were sequence discrepancies between reads. Genomic DNA was amplified in at least 50 individuals using 2.5 pmol each primer, 1.5 mM $MgCl_2$, 100 μM dNTPs, 0.75 μM AmpliTaq GOLD polymerase, and 19 ng DNA in a 15 μl reaction. Reactions were assembled using a PACKARD MultiPROBE robotic pipetting station and then put in MJ 96-well tetrad thermocyclers (96°C for 10 minutes, followed by 35 cycles of 96°C for 30 seconds, 59°C for 2

minutes, and 72°C for 2 minutes). A subset of the PCR assays for each individual were run on 3% NuSieve gels in 0.5X TBE to confirm that the reaction worked.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

31. (Amended) A method of [diagnosing or aiding in the diagnosis] determining increased likelihood of a vascular disease in [an individual] a human, comprising

[a) obtaining a nucleic acid sample from the individual; and

b)] determining the nucleotide present at nucleotide position 1186 of the thrombospondin-4 gene in a nucleic acid sample obtained from a human,

wherein presence of a C at nucleotide position 1186 is indicative of increased likelihood of a vascular disease in the [individual] human as compared with [an individual] a human having an G at nucleotide position 1186, thereby determining increased likelihood of vascular disease in a human.

36. (Amended) A method of [diagnosing or aiding in the diagnosis of] determining decreased likelihood of a vascular disease in [an individual] a human comprising

[a) obtaining a nucleic acid sample from the individual; and

b)] determining the nucleotide present at nucleotide position 1186 of the thrombospondin-4 gene in a nucleic acid sample obtained from a human, wherein presence of a G at nucleotide position 1186 is indicative of decreased likelihood of a vascular disease in the [individual] human as compared with [an individual] a human having a C at nucleotide position 1186, thereby determining decreased likelihood of a vascular disease in a human.